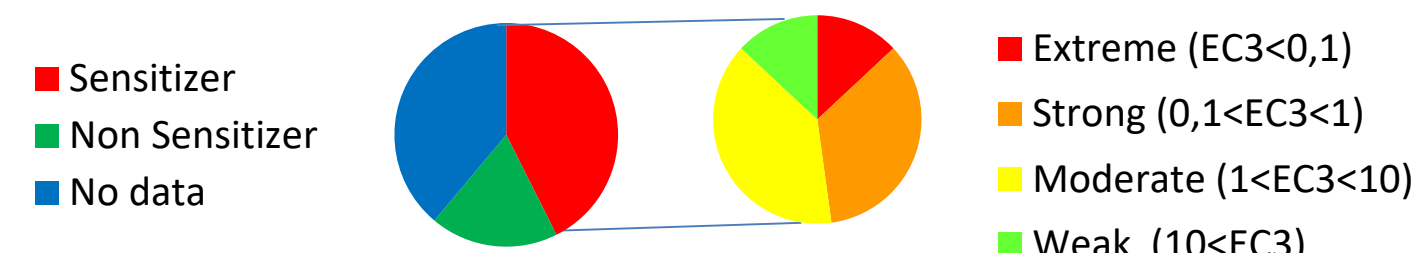


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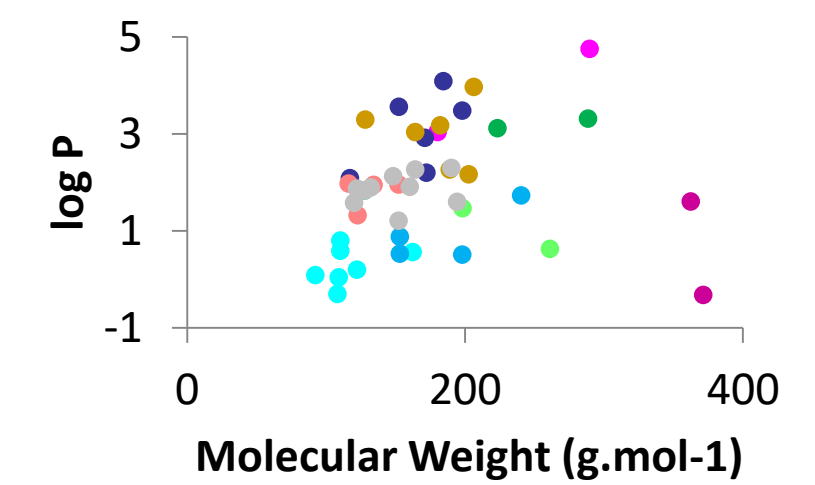
## Introduction

Understanding the bioavailability of chemicals is key to the safety assessment of topically applied chemicals. The Cosmetics Europe ADME Task Force is therefore evaluating and developing *in vitro* and *in silico* approaches to measure and predict the skin bioavailability of 50 cosmetics relevant chemicals. *In vitro* skin penetration was determined in *ex vivo* human skin. Metabolism was assessed in human liver and EpiSkin™ S9 and, for 10 chemicals, in fresh *ex vivo* human and pig (a waste product of the meat industry) skin. The kinetics of the reactivity of chemicals were measured in a modified DPRA assay – included to help with assessing skin sensitization, since 21 chemicals are known skin sensitizers. Additionally, partition and diffusion coefficients of chemicals in different skin layers were measured, with the intention to improve skin penetration *in silico* models.

## Project overview and results

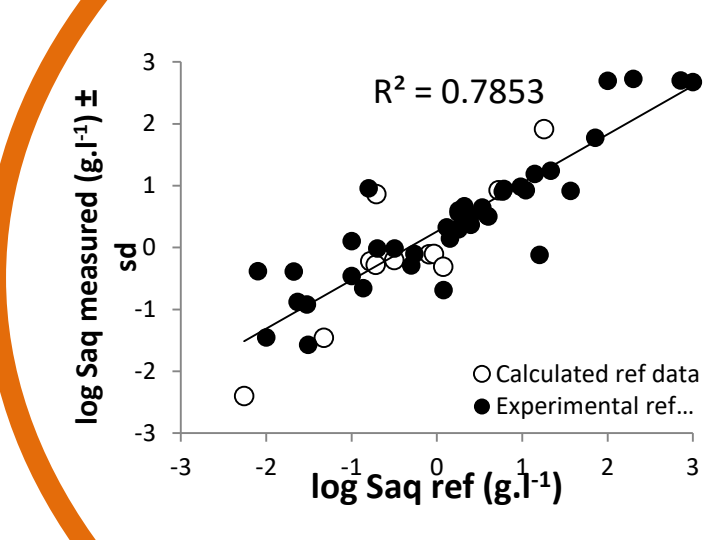


- ### Chemicals tested
- 50 chemicals in total
  - Large chemical space divided into 10 clusters based on physico-chemical properties (MW, log P, pKa, Sw)
  - Radiolabelled forms available
  - Solubility > 0.01 g.L<sup>-1</sup>



### Solubility

Protocol according to guidelines OECD 105 (Quantification with radioactivity)



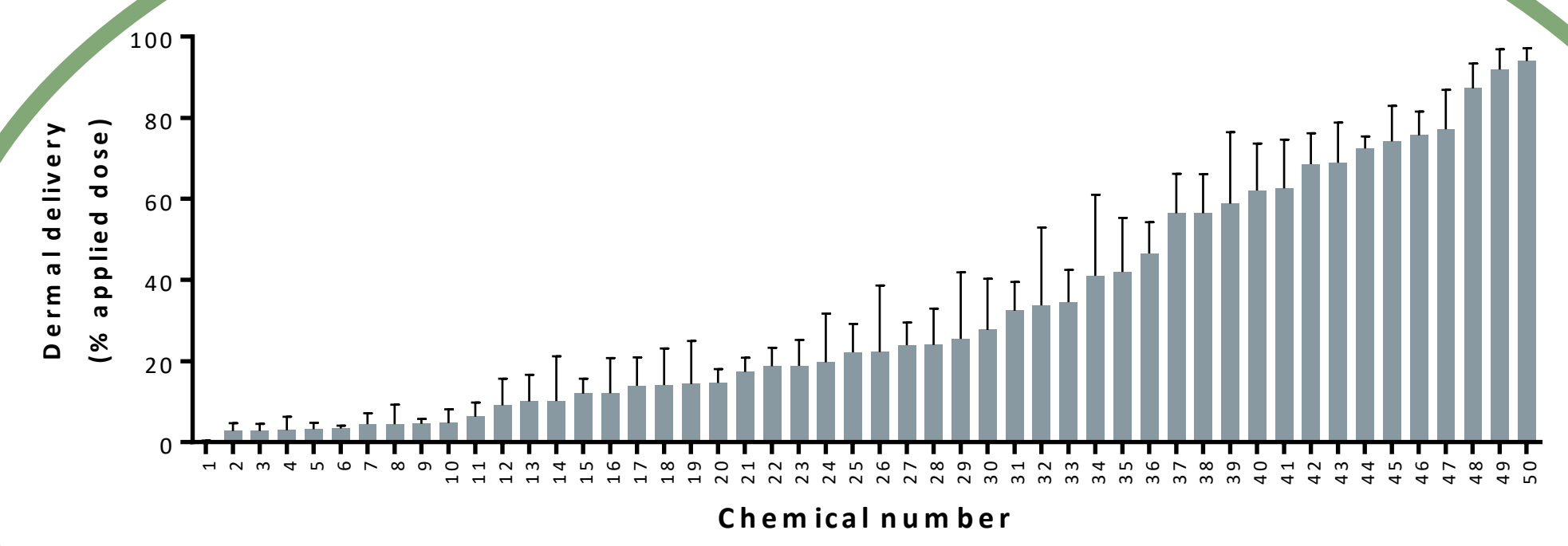
Solubility measured in:  
Acetone/Olive oil (4/1)  
Water  
DMSO  
Ethanol  
PBS 0.1M + 5% EtOH

Linked to LLNA assay

Used for cutaneous absorption assays

Good correlation between measured & calculated data

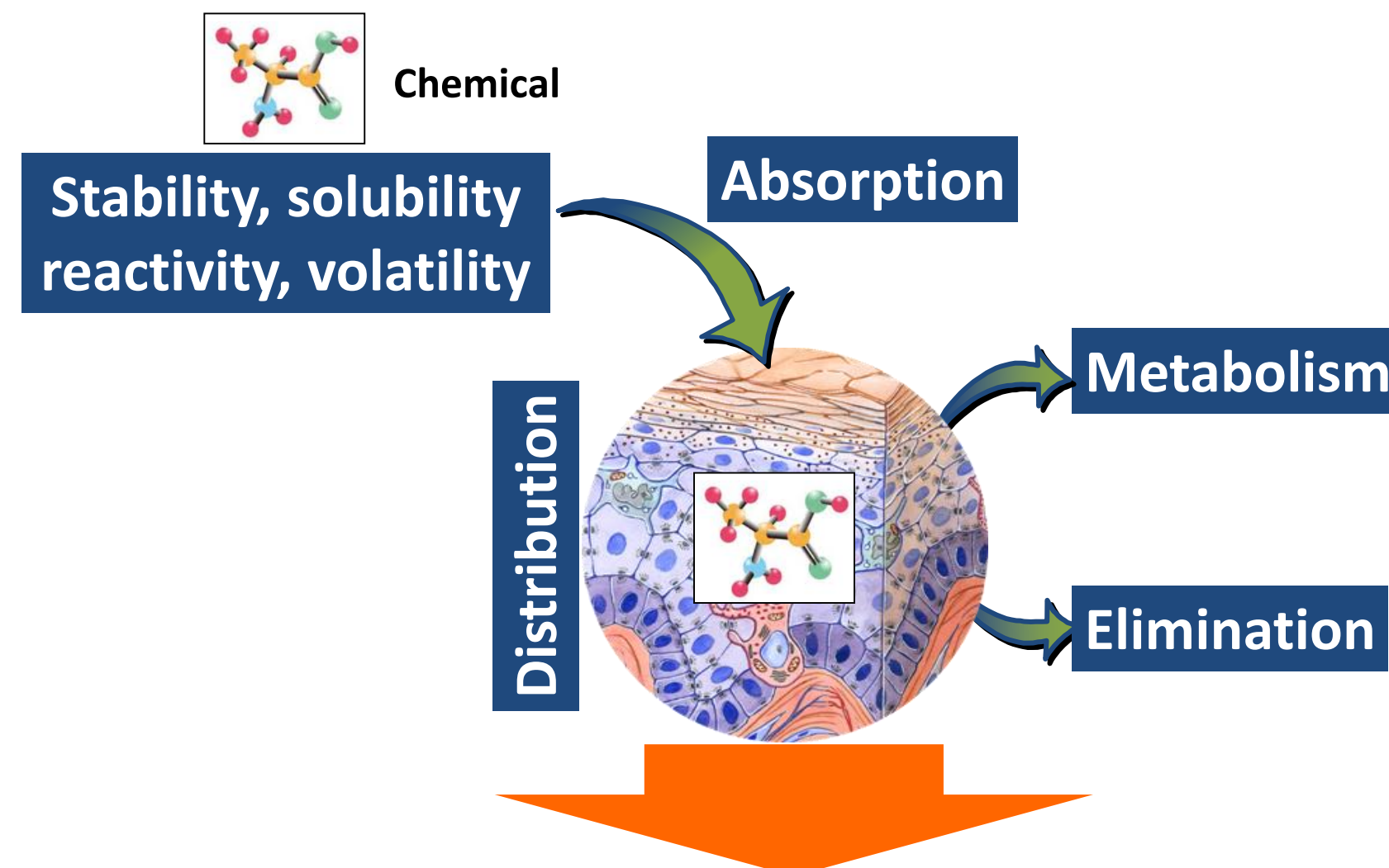
### Skin penetration



Range of gradually increasing dermal delivery values from 0.2% to 94% of the applied dose covered

## Data generation status

- Testing of up to 50 cosmetics relevant chemicals in different bioavailability assays is nearly complete
- Results provide relevant and standardized information on local skin and systemic concentrations of parent chemicals and their metabolites. These can be used in combination with PBPK models, cheminformatics and AOPs to refine the assessment of local and systemic toxicity of chemicals applied to the skin.



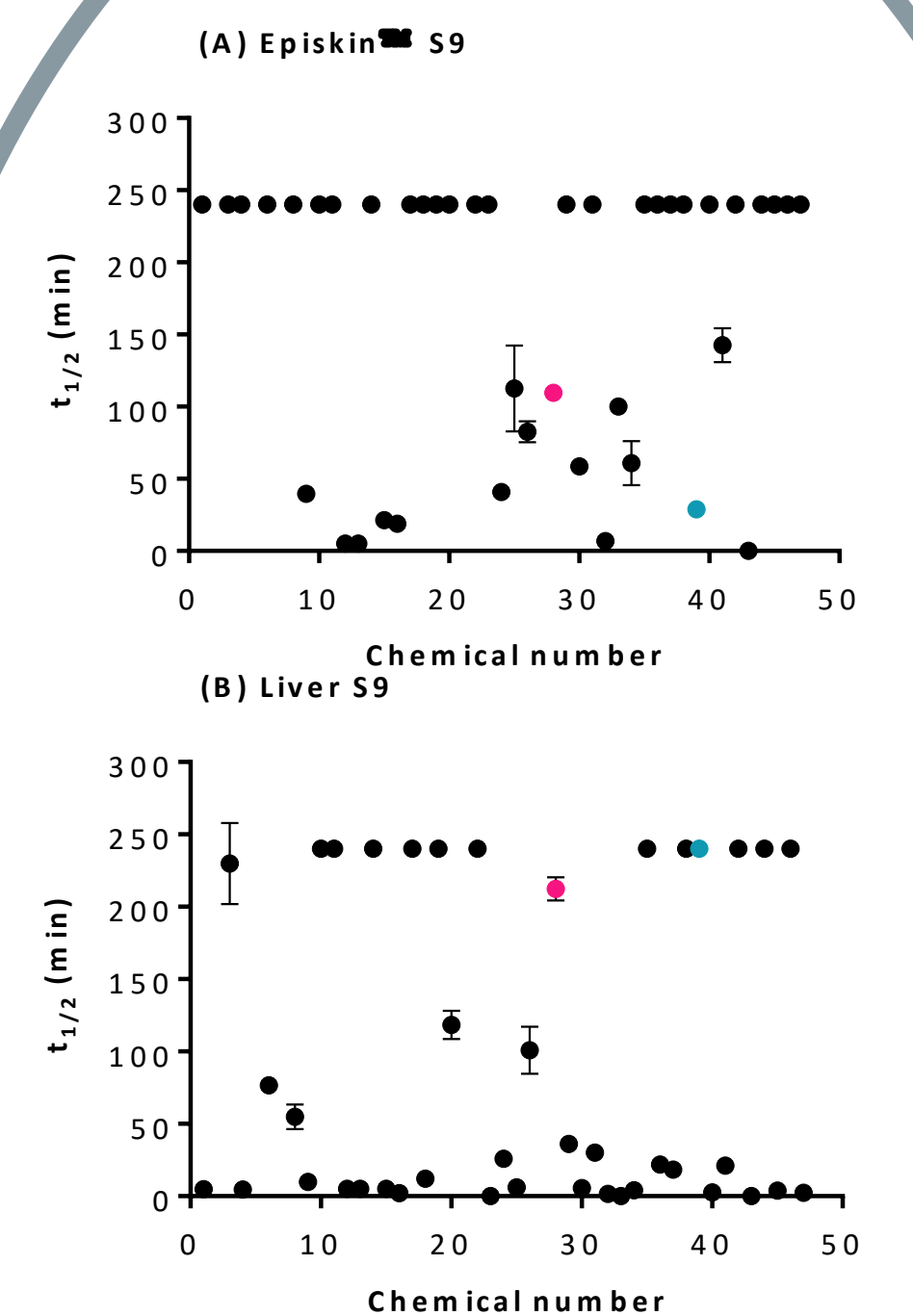
How are bioavailability parameters integrated to link with toxicological effects?

Option 1 : Use *in silico* model to predict skin absorption time profile

Option 2 : Use a statistical approach to integrate all measured parameters

Option 3 : Use simple relationship combining different parameters

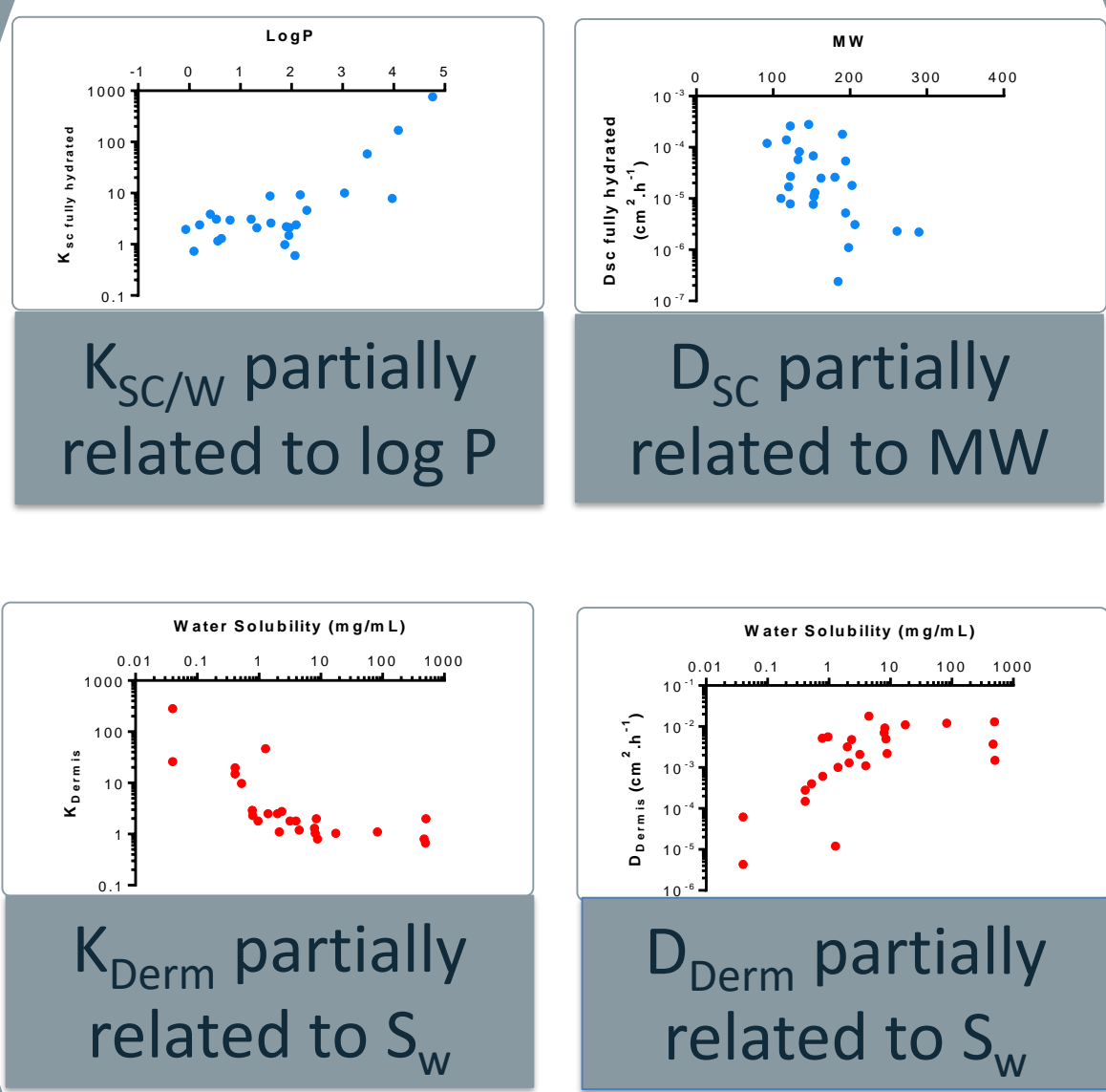
### Stability in skin and liver S9



Metabolism in Liver S9 generally higher than Skin S9

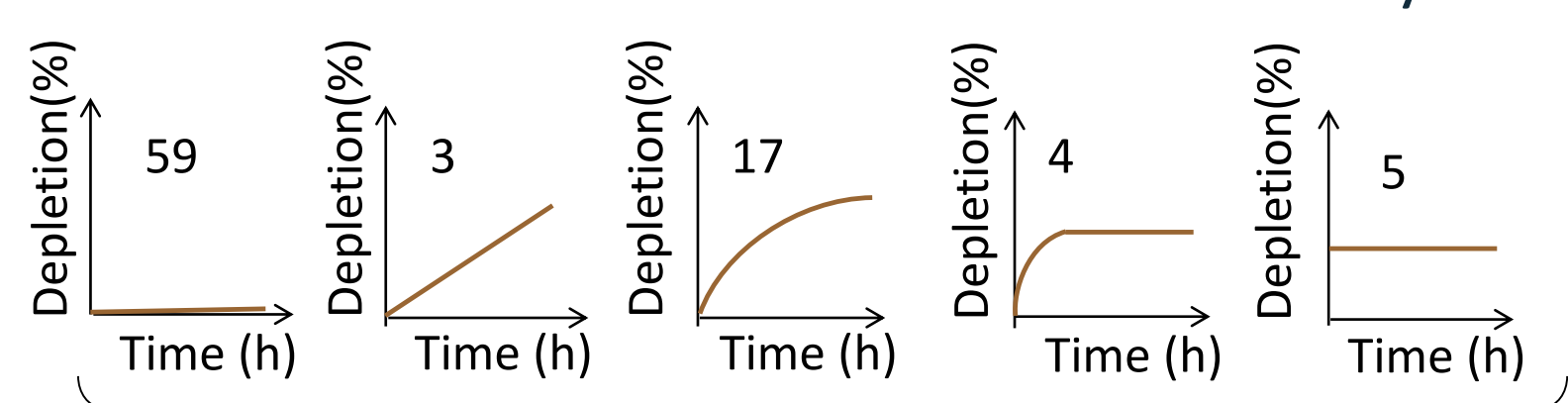
Exceptions: 4-aminophenol (pink) and Basic Red 76 (blue)

### Partition (K) & Diffusion (D) coefficients



### DPRA kinetics

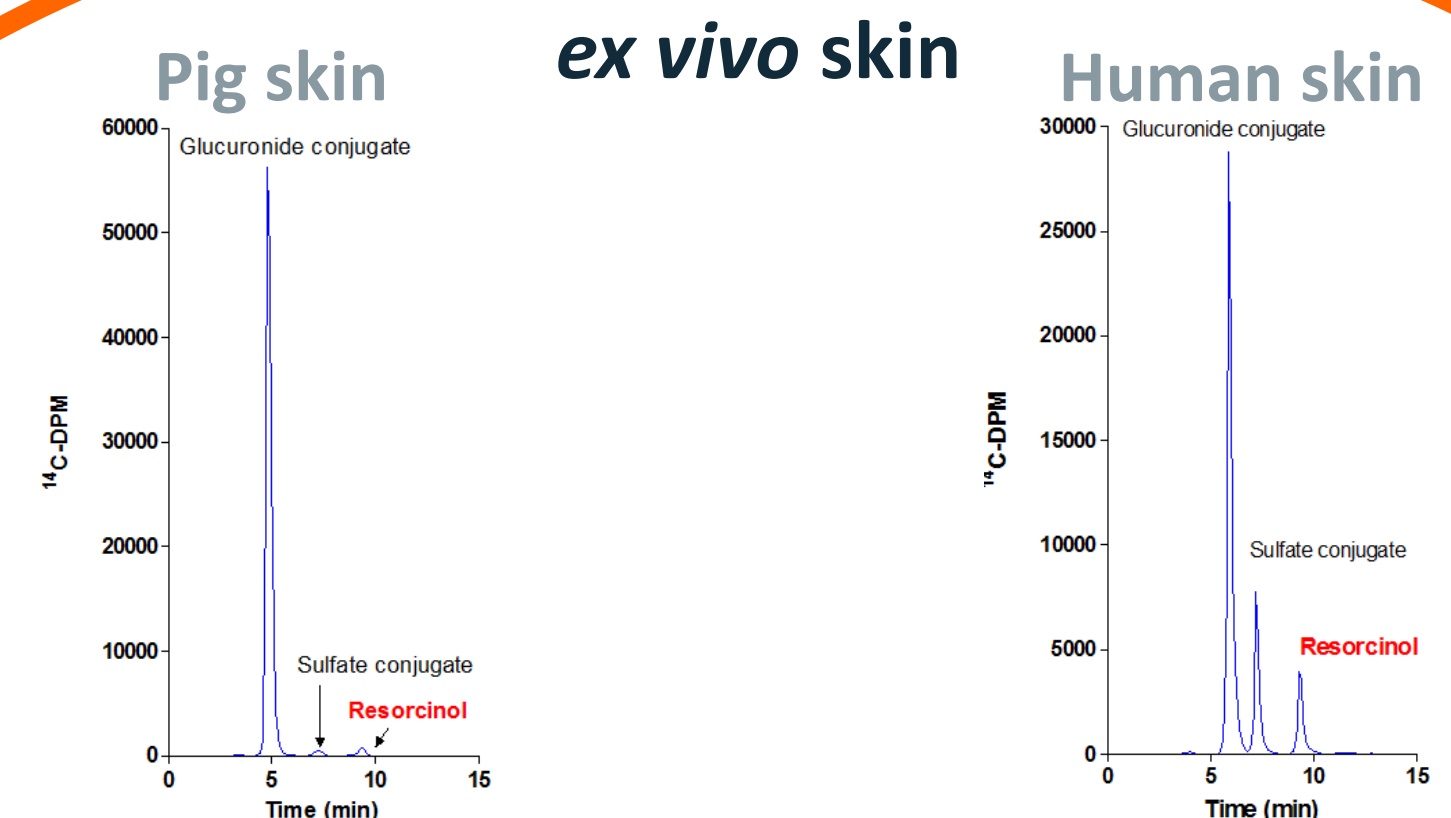
- Kinetic profiles measured for reactivity with lysine (LYS) and cysteine (CYS) peptides
- Most chemicals showed low reactivity with LYS or CYS



5 profiles consistent with theoretical curves (numbers denote number of chemicals that reacted with CYS and/or LYS with each kinetics profile) 1 unexpected profile

6 different kinetic profiles observed: link to skin sensitization?

### Metabolism in ex vivo skin



Sulfotransferases are a minor pathway in pig skin compared to human skin e.g. Resorcinol